Feasibility of neuromuscular electrical stimulation in critically ill patients☆☆☆

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ABSTRACT

Objective: Critically ill patients often develop intensive care unit–acquired weakness. Reduction in muscle mass and muscle strength occurs early after admission to the intensive care unit (ICU). Although early active muscle training could attenuate this intensive care unit–acquired weakness, in the early phase of critical illness, a large proportion of patients are unable to participate in any active mobilization. Neuromuscular electrical stimulation (NMES) could be an alternative strategy for muscle training. The aim of this study was to investigate the safety and feasibility of NMES in critically ill patients.

Setting: This is an observational study.

Patients: Fifty patients with a prognosticated prolonged stay of at least 6 days were included on day 3 to 5 of their ICU stay. Patients with preexisting neuromuscular disorders and patients with musculoskeletal conditions limiting quadriceps contraction were excluded.

Intervention: Twenty-five minutes of simultaneous bilateral NMES of the quadriceps femoris muscle. This intervention was performed 5 days per week (Monday-Friday). Effective muscle stimulation was defined as a palpable and visible contraction (partial or full muscle bulk).

Measurements: The following parameters, potentially affecting contraction upon NMES, were assessed: functional status before admission to the ICU (Barthel index), type and severity of illness (Acute Physiology And Chronic Health Evaluation II score and sepsis), treatments possibly influencing the muscle contraction (corticosteroids, vasopressors, inotropes, aminoglycosides, and neuromuscular blocking agents), level of consciousness (Glasgow Coma Scale, score on 5 standardized questions evaluating awakening, and sedation agitation scale), characteristics of stimulation (intensity of the NMES, number of sessions per patient, and edema), and neuromuscular electrophysiologic characteristics. Changes in heart rate, blood pressure, oxygen saturation, respiratory rate, and skin reactions were registered to assess the safety of the technique.

Results: In 50% of the patients, an adequate quadriceps contraction was obtained in at least 75% of the NMES sessions. Univariate analysis showed that lower limb edema (P < .001), sepsis (P = .008), admission to the medical ICU (P = .041), and treatment with vasopressors (P = .011) were associated with impaired quadriceps contraction. A backward multivariate analysis identified presence of sepsis, lower limb edema, and use of vasopressors as independent predictors of impaired quadriceps contraction (R² = 59.5%). Patients responded better to NMES in the beginning of their ICU stay in comparison with after 1 week of ICU stay. There was no change in any of the safety end points with NMES.

Conclusions: Critically ill patients having sepsis, edema, or receiving vasopressors were less likely to respond to NMES with an adequate quadriceps contraction. Neuromuscular electrical stimulation is a safe intervention to be administered in the ICU.

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1. Introduction

Outcome and survival rate of critically ill patients has improved over the last decades by new approaches of mechanical ventilation and advancements in critical care [1,2]. Nevertheless, the associated respiratory and multiorgan failure often necessitates a long intensive
care unit (ICU) stay, where invasive therapeutic modalities such as mechanical ventilation, circulatory support, and the use of sedative agents, neuromuscular blockers, corticosteroids or certain antibiotics will negatively affect muscle mass and force [3]. On top of that, these patients have reduced physical activity and are immobilized in their bed, which will further increase muscle catabolism and decrease muscle protein synthesis and muscle mass [4]. This muscle dysfunction is often referred to as intensive care unit–acquired weakness (ICU-AW) [4]. Intensive care unit–acquired weakness is associated with prolonged mechanical ventilation and increased mortality [5]. The consequences of ICU-AW may persist even years after ICU discharge, leading to impaired functional status and decrease in quality of life [3,6].

Muscle wasting starts early and fast, and the largest loss of mass and function occurs during the first 2 weeks of ICU stay [7], with a decrease of 17.7% in the first 10 days [8]. Therefore, it is important to prevent or attenuate this muscle deconditioning as early as possible in patients with expected prolonged bed rest. It has been demonstrated that early exercise training in critically ill patients receiving mechanical ventilation is feasible, safe, and beneficial for respiratory and limb muscles [9,10]. However, severely critically ill patients, often under the influence of sedative drugs, cannot collaborate in active exercise or muscle training. Neuromuscular electrical stimulation (NMES) is a treatment modality to evoke a muscle contraction through an electrical impulse via surface electrodes. For this technique, no patient cooperation is required. Recently, the application of NMES on the ICU has gained interest [11-15]. The effectiveness of NMES was studied during the “acute phase” of critical illness in several studies with very limited patient numbers. Some of these studies suggest beneficial effects on cross-sectional diameter loss of the quadriceps and decreased development of critical illness polyneuromyopathy [11,16]. Other studies, however, were unable to revert muscle wasting in the acute phase [12,13]. A review on NMES in acutely ill patients confirms this [17] but states that NMES is capable of preventing ICU-AW. Another review, however [18], shows that this evidence is not conclusive. The ability to elicit muscle contraction with NMES might be hampered due to myopathy [13,19], peripheral edema [20], sepsis [13], or medication [21]. All these factors were not considered in the previous studies on NMES in critically ill patients and might be important in the selection of patients and consequently the effectiveness of the intervention.

Rodriguez et al [14] reported that adequate muscle contractions (at least just palpable and visible) were observed in 77% of the sessions. However, differences between patients with a successful contraction and patients without contraction were not reported, and no explanation was given for this difference. Furthermore, ICU patients with edema were excluded from NMES in previous studies [12,15]. However, the ability to elicit a muscle contraction was never studied in ICU patients with edema [21]. In addition, questions may rise about the safety of NMES when an electrical current is applied to the critically ill patient. Only 2 studies reported heart rate, blood pressure, respiratory rate, and saturation during NMES [15,22]. Meesen et al [15] observed no changes in these parameters, whereas Gerovasili et al [22] found a small but statistically significant raise in heart rate and systolic blood pressure during NMES. However, the low number of patients in these studies does not allow final conclusions.

Therefore, this study was designed to investigate the feasibility and safety of NMES of the quadriceps femoris (QF) muscle in acute critically ill patients. The aims of the study were to assess the quality of the muscle contraction, to identify factors potentially interfering with the quality of the contraction, and to monitor the safety, that is, the effect of NMES on the cardiorespiratory function and the skin.

2. Materials and methods

2.1. Study design

This is a prospective cohort study to investigate the feasibility of NMES in eliciting a muscle contraction of the QF in critically ill patients. The study was conducted at the University Hospitals Leuven, Belgium, between November 2010 and November 2012. The medical ethical committee of the hospital approved the study. Written informed consent was obtained from all patients or a close relative in case of sedated or uncooperative patients.

2.2. Patients

On day 3 to 5 after admission to surgical and medical ICU, adult patients (≥18 years) with an expected prolonged stay of at least 3 more days at the ICU were enrolled in the study. An intensivist unrelated to the study judged whether the patient was expected to stay in the ICU for at least 3 more days. When a patient was not eligible on day 3 due to temporary exclusion criteria, daily reevaluation was performed and inclusion considered until the 5th day of admission to the ICU. If the patient did not receive an electrical stimulation session on day 3, 4, or 5, the patient could not be included anymore.

Exclusion criteria were readmission to the ICU, prognosticated lethal outcome, presence of a pacemaker, pregnancy, preexisting neurologic or neuromuscular disease (eg, Duchenne disease, myasthenia gravis, and spinal cord lesion), intracranial pressure more than 20 cm H2O, abnormal musculoskeletal, and skin conditions that could interfere with the stimulation (eg, femur fracture, burn wound on the thigh, and skin disease). Additional reasons for not starting the NMES were hemodynamic instability (mean arterial pressure <60 mm Hg), high fever (>39°C), inspired O2 fraction at least 60%, administration of neuromuscular blocking agents (NMBAs) in the last 24 hours, and severe agitation in a way that it was impossible to distinguish a painless NMES contraction from movement by the patient or pain by the NMES. These reasons for not starting the NMES session were in accordance with the UZ Leuven Start to Move ASAP guidelines at the start of the study.

2.3. Intervention

Patients underwent a transcutaneous NMES session during 5 days per week, from Monday to Friday. All patients received the highest standard conventional medical treatment and physical therapy during their stay at the ICU. The physical therapy program consisted of body positioning, chest physical therapy, active or passive upper and lower limb mobilization, and cycling in bed or in a chair adjusted to the individual needs of the patient. The intensity of the treatment was adjusted according to the clinical condition of the patient using the “Start-to-Move ASAP UZ Leuven protocol” guidelines [23].

Patients received simultaneous bilateral NMES (device, DUO 500: Gymna, Bilzen, Belgium) of the QF muscles, 5 days a week for 25 minutes per day until the day of discharge from the ICU. The maximal output of the device was limited at 80 mA. The patient was positioned in supine position with the head end of the bed 30° elevated. The legs were positioned in a neutral position, and a solid knee support roll was placed under the knees to achieve approximately 15° hip flexion and 30° knee flexion. Two self-adhesive surface electrodes (oval, 5 × 10 cm) were placed on the skin overlying the quadriceps muscle as depicted in Fig. 1.

To quantify the muscle contraction, a grading of the quality of contraction was designed (see First Online Supplement). The NMES session started with 5 minutes of warming up with an intensity to obtain a just palpable and visible contraction (type 3 in the First Online Supplement).
After 5 minutes of warming up, the actual NMES session (rectified alternating current; frequency, 50 Hz; intensity, 0-80 mA; pulse duration, 300-500 microseconds; series time, 8 seconds; series pause, 20 seconds; rise time, 2 seconds) was started. Now, a type 4 or 5 contraction (see First Online Supplement) was aimed to be achieved. When the patient tolerated the stimulation well and no good, visible, or palpable (type 4) contraction at the intensity of 60 mA was obtained, the pulse duration was increased to 400 microseconds. When this was still not sufficient to generate a type 4 contraction, the intensity of 60 mA was increased to 70 mA. The final steps to achieve a type 4 contraction were to increase the pulse duration to the maximum of 500 microseconds and to increase the intensity to the maximum of 80 mA. The intensity and/or pulse duration were adjusted 3 times: in the beginning, after 5 minutes (of warming-up), and after 15 minutes. Stimulation intensity and type of contraction (see First Online Supplement) were noted after 2.5, 10, and 20 minutes.

For all patients, the stimulation intensity was kept below the pain threshold. In fully sedated patients, we did not have sensory feedback to adjust the intensity accordingly. In the less sedated patients, facial expression was important to judge the increase in intensity. Awake patients were able to guide the intensity of the stimulation.

2.4. Measurements

2.4.1. Feasibility

During the first session, the characteristics of the patient were recorded: medical diagnosis, age, sex, weight, length, body mass index, the Acute Physiology And Chronic Health Evaluation (APACHE) II score, and the Barthel index for preadmission functional independence.

Each NMES session was initiated with an observation of the patient’s level of consciousness using the Glasgow Coma Scale (GCS), Score of 5 Questions (SSQ) (5 simple commands to check whether the patient was cooperative. For every correct response, the patients received 1 point. The questions were (1) open/close your eyes, (2) look at me, (3) open your mouth and put out your tongue, (4) nod your head and (5) raise your eyebrows when I have counted up to 5 [24], and the Sedation Agitation Scale (SAS) [25]. The level of edema of the lower limbs was measured using the classification added in the Second Online Supplement. This was performed by the person administering the electrical stimulation, just before the start of the NMES session by pressing the index finger on the middle of the quadriceps muscle and see how long it took for the skin to come back to its normal form. To define sepsis, the Bone criteria were applied [26]. Use of the following medication was recorded: corticosteroids, vasopressors, inotropes, aminoglycosides, and NMBAs.

To detect whether patients responded better to NMES in the beginning of their ICU period, a comparison of the type of contraction between session 1 and session 5 was performed. Furthermore, a correlation analysis between the degree of edema and the type of contraction was performed for its clinical importance.

In a subgroup of patients (n = 26), nerve conduction studies (NCS) and electromyography (EMG) were performed on the day of inclusion and every 7 days from then on as long as the patient stayed on the ICU by electrophysiologists not related to the ICU. The NCS/EMG did not take place during the NMES session. The results of the NCS and/or EMG might contribute to the prediction of successfully eliciting a contraction. The compound muscle action potential (CMAP), sensory nerve action potential (SNAP), and the spontaneous electrical activity (SEA) were investigated. For the CMAP, the median and tibial nerves were tested. The ulnar and peroneal nerves were tested when the aforementioned nerves were not testable. The CMAP was classified as abnormal when the amplitude reached or dropped below the absolute lower limit of normal in the 2 nerves. For the SNAP, the same definition of normality was set for the sural and median nerve. If it was unable to test the median nerve, the radial nerve was used. Spontaneous electrical activity was defined as presence of fibrillation potentials and/or positive sharp waves in at least 2 muscles located in at least 2 limbs. The muscles considered for this analysis were biceps brachii (if impossible, deltoid muscle) and extensor digitorum communis (if impossible, interosseus digitorum muscle) for the upper limbs. For the lower limbs, the gastrocnemius muscle (if impossible, tibialis anterior) and the vastus lateralis (if impossible, vastus medialis or rectus femoris) were used.

2.4.2. Safety

The patients’ cardiorespiratory responses (heart rate, blood pressure, oxygen saturation, and breathing frequency) are continuously measured and were recorded at the start and after 20 minutes of NMES. After stimulation, skin responses (redness, local edema, and skin etching) were observed by the person who performed the NMES.

2.5. Statistical analysis

2.5.1. Feasibility

To assess potential differences between patients with a positive response to NMES (contraction type 4 or 5; see First Online Supplement) and those with a lesser or no response (contraction type 1-3), the results were divided in “responders” and “non-responders.” Patients were qualified as responders if in at least 75% of the NMES sessions, an effective contraction (type 4 or 5) was detected. Otherwise, patients were classified as nonresponders. To investigate how many successful sessions were performed per patient, continuous analysis of the data was also performed. For edema, a score of 0 (see Second Online Supplement) was classified as no edema, a score of 1 to 4 was classified as edema. As for contraction, also for edema, 75% or more of the sessions had to have a score of 0 to be classified as having no edema.
Analyses of the use of corticosteroids, vasopressors, inotropes, aminoglycosides, and NMBAs were dichotomous. To be noted as administered, the medication should have been administered before inclusion or during the study period. Analysis of administered dose of medication showed similar results as the dichotomous results. The only results shown are the latter results.

To investigate whether a contraction was obtained more successfully in the beginning of the patients’ ICU stay, a comparison between session 1 and session 5 was performed. An effective response was defined as a contraction type 4 or 5 (see First Online Supplement). On the dichotomous data, a χ² test was performed.

Continuous variables with normal distribution were reported as mean and SD. Independent t tests were performed to evaluate the differences between responders and nonresponders. For data not normally distributed, median and interquartile range were reported, and differences were examined using Mann-Whitney U test. Categorical variables are presented as numbers and percentage (%). χ² test was used to evaluate the differences between the responder and the nonresponder group.

Multivariate analysis (backward stepwise) was performed to identify which factors could contribute to the explanation in the response to NMES. All variables in univariate analysis with \( P < .15 \) were considered as having a potential contribution in the multivariate analysis. For all these variables, collinearity was explored. When 2 variables were significantly correlated, a bivariate regression analysis was performed to identify significant contribution of the variables to the model. If only 1 of the 2 variables had a significant contribution, the nonsignificant variable was excluded in the multivariate analysis due to collinearity. Furthermore, not more than 1 variable per 10 observations was included in the multivariate model. This selection criterion has been used before by Sharshar et al [27].

2.5.2. Safety

Averages in heart rate, blood pressure, oxygen saturation, and respiratory rate were calculated per patient before the start of the NMES session and after 20 minutes of electrical stimulation. These values were compared using a paired t test to detect changes before and at the end of the NMES sessions.

The statistical significance of \( P \) value was set at .05. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 19.0; SPSS Inc, Chicago, IL).

3. Results

3.1. Feasibility

Fifty patients were included in the feasibility study. The same 50 patients were used to investigate safety of NMES. The flow chart is depicted in Fig. 2. On day 3, 23 patients were included, 14 patients were included on day 4, and the remaining 13 were included on day 5. The patients’ average ICU length of stay was 15 days. Because of one or more of the temporary instabilities (fraction of inspired oxygen, >60%; respiratory rate, >30/min; and temperature, >39°C) and absence of the patient due to other investigations or surgery, 346 sessions (7 sessions per patient) were performed. Six of these sessions had to be terminated prematurely due to inconvenience and agitation of the patient after starting the NMES session.

Twenty-five patients (50%) were responders, whereas 25 patients (50%) were nonresponders. This is depicted in Fig. 3. The differences between responders and nonresponders are depicted in Table 1. Patients with sepsis (\( P < .001 \)), edema (\( P < .001 \)), and those receiving vasopressors (\( P = .011 \)) were more frequently classified as nonresponders. Furthermore, patients admitted to the medical ICU were less likely to be responder compared with patients admitted to the surgical intensive care unit (SICU) (\( P = .041 \)).

A statistically significant difference was found for the type of contraction between session 1 and session 5 (\( P = .005 \) (n = 23)).

No patient had a negative response (contraction type 1-3) in session 1 that changed to a positive response (contraction type 4-5) in session 5. In contrast, 22% of the patients changed from a positive response in session 1 to a negative response in session 5.

In the univariate analysis, sepsis, edema, admission category, medical intensive care unit (MICU) or SICU, corticosteroids, and vasopressors had \( P < 0.15 \). Edema and sepsis were correlated, but both contributed significantly to the bivariate model and were retained in the multivariate analysis. Corticosteroids were eliminated due to collinearity with edema, and MICU/SICU was eliminated due to collinearity with admission category and sepsis. Consequently, multivariate analysis was performed including sepsis, edema, vasopressors, and admission category in the model. The backward stepwise multivariate regression analysis withheld sepsis, edema, and vasopressors in the equation. The explained variance (\( R^2 \)) was 59.5%. These results are shown in Table 2.

The possibility to elicit an adequate contraction could not be predicted by the NCS and EMG. The \( P \) values between type of contraction after the NCS/EMG and CMAP (\( P = 1.000 \)), SNAP (\( P = .367 \)), and SEA (\( P = .422 \)) did not reach statistical significance.

When comparing the level of edema with the type of contraction per session, a significant difference (\( P < .001 \)) was found as shown in Table 3. An inverse relationship can be found between the level of edema and the type of contraction. Patients with no or almost no edema (level 1 and 2) were more prone to have a good response to the NMES (type 4 or 5 contraction). Patients with considerable edema (level 3 and 4) were more likely to have a poor or no response to NMES (type 1-3 contraction). Furthermore, patients with a level 4 edema never had a contraction type 3 or more.

3.2. Safety

The cardiovascular and respiratory responses are depicted in Table 4. None of the investigated parameters changed significantly. Immediately after the stimulation, a red skin under the electrodes was observed in 50% of the stimulation sessions. This redness gradually disappeared after the NMES session without detrimental responses of the skin.

4. Discussion

4.1. Feasibility

Neuromuscular electrical stimulation is a treatment modality aiming to preserve muscle mass and strength. In this study, it was
shown that successful contractions were obtained in 50% of the included patients. Edema, sepsis, and administration of vasopressors negatively influenced the quality of the muscle contraction induced by NMES.

The application of NMES in critically ill patients is attractive because specifically, in the early phase, selective type II atrophy and an up-regulation of “atrophy genes” in type IIA fibers were observed [21]. Interestingly, the recruitment order of muscle fibers during NMES may specifically enhance contractions of the fast (type II) fibers [28] and thus might theoretically counteract this process. In our study, 50% of the patients were classified as responders. To our knowledge, only Rodriguez et al [14] reported a success rate of 77% in patients with sepsis. This is higher than our 50% success rate and might be related to the definition of “responders.” Rodriguez et al [14] reported a just visible contraction as a good response to the stimulus. In our scoring, this corresponds to a type 3 contraction and would “not” be sufficient to be a responder. The choice for a minimal response type 4 contraction in our study was set because of the expected dose-response relationship of the stimulus. Snyder-Mackler et al [29] found that a higher intensity of muscle contraction during NMES resulted in more improvement in muscle function. Therefore, it could be expected that a type 4 or 5 contraction is more beneficial for the patient.

No differences were found in administration of NMBA and aminoglycosides between the responder and nonresponder group. Neuromuscular blocking agents are known to block the neuromuscular transmission at the neuromuscular junction by inhibition of acetylcholine. No stimulation was provided to patients who had NMBA administration in the 24 hours preceding the NMES session. Because no differences were found between the 2 groups, there seems to be no negative long-term effects of NMBA on muscle contractility. All patients treated with NMBA got the NMBA administered in the first 48 hours on the ICU. Papazian et al [30] also did not find an effect of early NMBA on the incidence of muscle weakness later in the ICU. De Jonghe et al [31] stated that the use of aminoglycosides alone is not related with ICU-AW, but it is related with sepsis, which is a major risk factor for ICU-AW. This is in accordance with our findings. Sepsis and aminoglycosides were found to be collinear, and only sepsis contributed significantly to the bivariate model. Statistically significant differences

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**Table 1**

Baseline characteristics of responders and nonresponders

<table>
<thead>
<tr>
<th>Main diagnosis</th>
<th>Responders (n = 25)</th>
<th>Nonresponders (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, n (%)</td>
<td>15 (60)</td>
<td>11 (44)</td>
<td>.258</td>
</tr>
<tr>
<td>Age, y (mean ± SD)</td>
<td>58 ± 13</td>
<td>62 ± 10</td>
<td>.166</td>
</tr>
<tr>
<td>Height, meter (mean ± SD)</td>
<td>1.70 ± 0.09</td>
<td>1.69 ± 0.11</td>
<td>.711</td>
</tr>
<tr>
<td>Weight, kg (mean ± SD)</td>
<td>73 ± 16</td>
<td>74 ± 16</td>
<td>.899</td>
</tr>
<tr>
<td>BMI, kg/m² (mean ± SD)</td>
<td>25.1 ± 43</td>
<td>25.9 ± 5.5</td>
<td>.584</td>
</tr>
<tr>
<td>Admission category:</td>
<td></td>
<td></td>
<td>.093</td>
</tr>
<tr>
<td>Abdominal/pelvic surgery (n)</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery (n)</td>
<td>2 (8)</td>
<td>4 (16)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal/hepatic disorder (n)</td>
<td>8 (32)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure (n)</td>
<td>3 (12)</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>Organ transplantation (n)</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Thoracic surgery (n)</td>
<td>0 (0)</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>Hematology/oncology (n)</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other diagnosis (n)</td>
<td>2 (8)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Sepsis, yes, n (%)</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Barthel index (score)</td>
<td>18 ± 3</td>
<td>18 ± 2</td>
<td>.944</td>
</tr>
<tr>
<td>APACHE II score (0-70)</td>
<td>25 ± 8</td>
<td>27 ± 6</td>
<td>.578</td>
</tr>
<tr>
<td>GCS (0-15)</td>
<td>7 ± 3</td>
<td>9 ± 3</td>
<td>.216</td>
</tr>
<tr>
<td>SSQ (0-5)</td>
<td>2 ± 1</td>
<td>3 ± 2</td>
<td>.162</td>
</tr>
<tr>
<td>SAS (1-7)</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
<td>.266</td>
</tr>
<tr>
<td>Intensity, mA</td>
<td>65 ± 8</td>
<td>69 ± 13</td>
<td>.236</td>
</tr>
<tr>
<td>No. of sessions/patient</td>
<td>5 ± 4</td>
<td>8 ± 7</td>
<td>.152</td>
</tr>
<tr>
<td>Medical ICU, n (%)</td>
<td>6 (24)</td>
<td>13 (52)</td>
<td>.041</td>
</tr>
<tr>
<td>Edema, yes, n (%)</td>
<td>10 (40)</td>
<td>23 (92)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Corticosteroids, yes, n (%)</td>
<td>12 (48)</td>
<td>18 (72)</td>
<td>.114</td>
</tr>
<tr>
<td>Vasopressors, yes, n (%)</td>
<td>16 (64)</td>
<td>24 (96)</td>
<td>.011</td>
</tr>
<tr>
<td>Inotropes, yes, n (%)</td>
<td>6 (24)</td>
<td>8 (32)</td>
<td>.588</td>
</tr>
<tr>
<td>Aminoglycosides, yes, n (%)</td>
<td>9 (36)</td>
<td>12 (48)</td>
<td>.355</td>
</tr>
<tr>
<td>NMBA, yes, n (%)</td>
<td>11 (44)</td>
<td>12 (48)</td>
<td>.879</td>
</tr>
</tbody>
</table>

BMI indicates body mass index. APACHE II score, Acute Physiology And Chronic Health Evaluation; SSQ, score on 5 questions; SAS, Sedation Agitation Scale; ICU, intensive care unit; NMBA, neuromuscular blocking agents.

Results are expressed as mean ± SD for t test and Mann-Whitney U test. Numbers are used for χ². Barthel index is a score ranging from 0 to 20. APACHE II score from 0 to 70, GCS from 0 to 15, SSQ from 0 to 5, and SAS from 1 to 7.

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**Table 2**

Stepwise backward multivariate analysis: variables in the model (see text for selection method): sepsis, edema, vasopressors, and admission category

<table>
<thead>
<tr>
<th>Main diagnosis</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>0.105 (0.020-0.536)</td>
<td>.003</td>
</tr>
<tr>
<td>Edema</td>
<td>0.118 (0.017-0.804)</td>
<td>.016</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>0.076 (0.005-1.067)</td>
<td>.028</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval. Probability for stepwise entry, 0.05 and removal, 0.10. R²: 0.595.
of a muscle contraction, with the inability to obtain a type 3, 4, or 5 contraction if a level 4 edema is present. Harper et al [37] observed that, in ICU patients with limb edema, a higher intensity was needed to obtain the same contraction. However, this high intensity is often impossible to achieve due to the sensory discomfort [38]. In addition, edema contributed to an increased distance between electrodes and muscle [20], which in turn might reduce current density and impair muscle contraction. Therefore, palpation was used in addition to the visual inspection to minimize this type of bias.

Analysis showed that 22% of the patients with a good response (type 4 or 5) in session 1 did not respond well (type 1-3) anymore in session 5. This can be attributed to a change in parameters such as development of edema or sepsis in the first days on the ICU. Because this was not investigated in this study, this can only be assumed and should be investigated in critically ill patients to make solid conclusions on this result.

4.2. Safety

Neuromuscular blocking agents can be applied safely as none of the cardiorespiratory parameters changed significantly. This was also found by Meesen et al [15]. The change in heart rate in our patients did not reach statistical significance but showed a P = .057. The actual change, however, is only one beat per minute. A small but significant change in heart rate has also been found by Gerovasili et al [22]. The raise of 5 beats per minute was concluded to be a clinically irrelevant change. This is in accordance with the change in results presented in this article.

The skin showed redness under the electrode in 50% of the cases immediately after stimulation. This, however, disappeared gradually after the NMES session and can be considered local hyperemia due to the NMES. None of the patients reported negative consequences after the NMES.

4.3. Limitations of the study

The cut-off to determine whether a patient was a “responder” was set as “a good contraction in 75% of the sessions.” This cut-off was set because a minimum of at least 4 stimulation sessions (the third day and the 3 more days on the ICU) was considered as a potential minimal effective stimulation. Although a dose-response relationship has been shown, no data exist on a minimal contraction or minimal number of sessions needed to prevent muscle atrophy in the critically ill patient. To be a responder, at least 3 of these 4 sessions should be performed with a type 4 or 5 contraction. If the patient had to stay in the ICU longer, the same 75% limit was maintained. If patients with type 3 (or less) contraction do not have an effect after NMES, however, should still be investigated.

The intensity on our stimulator was limited at 80 mA. It is possible that an increase in maximal intensity above 80 mA resulted in fewer nonresponders. However, literature on NMES in critically ill patients reports intensity ranges below 80 mA, namely, 19 to 55 mA [11], 40 to 80 mA [22], and below 54 mA [13]. Our mean intensities (65 mA for the responder group and 69 mA for the nonresponder group) must be considered high intensity.

With our device, we were limited to use 2 electrodes with the standardized positioning of the electrodes as described in the methods section. However, when no contraction was obtained, the distal electrode was replaced to obtain a better muscle contraction. However, this was never the case. The possibility remains, however, that a higher rate of responders would have been obtained with more electrodes on the different motor points of the quadriceps.

Because this is the first study to investigate the quality of the muscle contraction, a self-made classification was developed to quantify the contraction. The 4-point classification provides a clear distinction between the different types of contraction to optimize the interrater reliability. Three physiotherapists performed the stimulation sessions; however, most observations (71%) were performed by one researcher (JS).

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Table 3
Degree of edema and type of contraction per session for all patients (n = 50)

<table>
<thead>
<tr>
<th>Contraction type 1</th>
<th>Contraction type 2</th>
<th>Contraction type 3</th>
<th>Contraction type 4</th>
<th>Contraction type 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema type 0</td>
<td>30</td>
<td>4</td>
<td>15</td>
<td>67</td>
</tr>
<tr>
<td>Edema type 1</td>
<td>21</td>
<td>13</td>
<td>30</td>
<td>88</td>
</tr>
<tr>
<td>Edema type 2</td>
<td>28</td>
<td>14</td>
<td>44</td>
<td>16</td>
</tr>
<tr>
<td>Edema type 3</td>
<td>18</td>
<td>7</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Edema type 4</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The explanation of contraction type and edema type can be found in Online Supplement 1 and 2.

Results are statistically significant (P < .001).

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Table 4
Cardiovascular and respiratory responses during NMES for all patients (n = 50)

<table>
<thead>
<tr>
<th></th>
<th>Pre NMES session</th>
<th>After 20 min of NMES</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats per minute)</td>
<td>89 ± 13</td>
<td>90 ± 14</td>
<td>.057</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130 ± 16</td>
<td>131 ± 15</td>
<td>.561</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>64 ± 8</td>
<td>65 ± 10</td>
<td>.342</td>
</tr>
<tr>
<td>O2 saturation (%)</td>
<td>97 ± 2</td>
<td>97 ± 3</td>
<td>.598</td>
</tr>
<tr>
<td>Respiratory rate (beats per minute)</td>
<td>20 ± 3</td>
<td>20 ± 4</td>
<td>.742</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD.
4.4. Clinical implications

This study identified patient characteristics (sepsis, edema, vasopressors, and the admittance to MICU) that might impede with the generation of a sufficient muscle contraction by electrical muscle stimulation. It is extremely important for future interventional studies to understand that not every patient will respond similarly to stimulation.

Future studies should include stimulation of the different motor points to optimize contraction. Furthermore, the stimulator should be able to reach higher maximal intensities to increase the probability of obtaining a contraction. In the analysis of the results, it should also be examined whether a responder or nonresponder affects results of NMES.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2014.06.024.

References


